A CLINICAL ASSESSMENT OF THE QUADRUPLE COMBO INCLUDING EPLERENONE, IVABRADINE, CLOPIDOGREL, ROSUVASTATIN IN 144 HUMAN SUBJECTS WITH OVERT HEART FAILURE

ADRIAN TASE[1], MONICA ȚÂNȚU[2], MIHAI POPESCU[3]

[1,2,3]*Emergency County Hospital Pitești, University of Pitești*

Keywords: *quadruple combo, heart failure, biomarkers, continuum*

Abstract: *Aim. An assessment of the quadruple combo eplerenone, ivabradine, clopidogrel, rosuvastatin behaviour in heart failure, in terms of clinical pharmacology, in order to use it, eventually, on a large scale in cardiovascular prevention vs. 288 controls. Method. 144 patients with heart failure documented by biomarkers, treated 6 months with the quadruple combo. Results. The combo proved high efficacy in clinical, haemodynamic, imaging, quality-of-life terms and safety. Conclusions. The combo could be used on larger scale in benefit of cardiovascular patients along the cardiovascular continuum.*

Cuvinte cheie: *combinaţie cvadruplă, insuficienţă cardiacă, biomarkeri, continuum*

Rezumat: *Obiectiv. Evaluarea în termeni de farmacologie clinică a comportamentului combinaţiei cvadruple eplerenonă, ivabradină, clopidogrel, rosuvastatină în insuficienţa cardiacă în vederea eventualei sale utilizări pe scară largă în prevenţia bolilor cardiovasculare. Metodă. Am studiat retrospectiv 144 pacienţi cu insuficienţă cardiacă manifestă, cu biomarkeri pozitivi, trataţi 6 luni cu combinaţia cvadruplă vs. 288 pacienţi din lotul de control. Rezultate. Combinaţia se dovedeşte eficientă terapeutic în termeni clinici, hemodinamici, imagistici, de calitate a vieţii şi prezintă siguranţă în administrare. Concluzii. Combinaţia cvadruplă ar putea fi folosită pe scară mai largă în beneficiul pacienţilor cardiovasculari de-a lungul continuum-ului cardiovascular.*

INTRODUCTION

In the last decade, within our geographical area, the Argeş county, the prevalence and severity of heart failure (HF) registered a steady increment, and subsequently a higher number of admissions. In order to face this challenge, we currently use HF biomarkers like NT-proBNP, and a pharmacological armamentarium including a mineralocorticoid receptor blocker, an iF channel inhibitor, a platelet P_2Y_{12} receptor blocker, a HMG-CoA reductase inhibitor.

In the same region, there is also a growing prevalence of arterial hypertension, diabetes mellitus, dislipidemia, smoking habit, actually the major risk factors of acute myocardial infarction.

Therefore, in terms of prevalence, the two terminals of the cardiovascular (CV) continuum V. Dzau – E. Braunwald display quite similar behaviour.

PURPOSE

Starting from these premises, we performed a study aiming to assess by clinical means the therapeutic efficacy, tolerability and safety, drug interactions in vivo etc., of four pharmacological agents: eplerenone, ivabradine, clopidogrel, rosuvastatin, administered concomitantly in CV patients receiving permanent pharmacological therapy prescribed in our clinical division. If this quadruple combination proves efficacy and tolerability in HF terminal, it could be extrapolated, in primary prevention, at the other terminal of the Dzau & Braunwald CV continuum.

METHODS

The 6-month study included 144 patients admitted in the Clinical Division of Cardiology, Emergency Hospital County Arges within 01/JAN/2008 – 31/DEC/2010, who gave written consent concerning the participation and were selected by the following criteria:

Inclusion Criteria:

- Subjects of both genders, age 18-75 years old;
- Main diagnosis: HF NYHA III or IV classes, documented by clinical significant values of specific biomarkers, coronary artery disease aetiology, with or without former myocardial infarction, with or without angina pectoris CCS (Canadian Cardiac Society) II-IV classes;
- Qualifying values of NT-pro-BNP biomarkers for the diagnosis of HF;
- Sinus rhythm;
- Pharmacologic therapy including eplerenone, ivabradine, clopidogrel, rosuvastatin, associated or not with other drugs prescribed for various CV and non-CV co-morbidities.

Exclusion Criteria:

- Normal values of biomarker NT-pro-BNP;
- Chronic hepatitis or hepatic cirrhosis, taking into consideration that the liver plays an important role in drugs' pharmacokinetics, and its injury leads to metabolic/excretion abnormalities. In addition, in chronic liver diseases the clinical use of rosuvastatin is not recommended;
- Renal insufficiency with creatinin clearance < 30 mL/min, taking into account that the kidney plays a major role in drug pharmacokinetics, its derangement leading to metabolic/excretion abnormalities;
- Atrial fibrillation, a clinical setting of non-indication for ivabradine, and/or severe arrhythmias with vital risk;
- Serum K^+ values > 5,5 mEq/L, a clinical setting within eplerenone administration must be cautious;

[1]Corresponding author: Adrian G. Tase, Aleea Spitalului, Nr. 36, 110084, Pitești, România, E-mail: agtase@yahoo.com, Tel: +40248 287150
Article received on 02.08.2013 and accepted for publication on 14.10.2013
ACTA MEDICA TRANSILVANICA December 2013;2(4):242-244

- Major psychopathies, because we cannot rely on a responsible and disciplined behaviour of such patients;
- Diseases with low survival hope, e.g. cancers in evolution.

The study group displays the following demographic features:

- Mean age 67,5 +/- 9,2 years;
- Male predominance 61,14%;
- All of caucasian race.

The CV variables of study subjects are dynamically presented in results section. These subjects were administered therapeutically the original formulations of eplerenone, ivabradine, rosuvastatin, clopidogrel, +/- other drugs, at the discretion of the physician, depending on CV and non-CV co-morbidities (table no. 1).

Table no. 1. Medication administrated therapeutically

Active substance	Commercial name	Daily dosage
Eplerenone	Inspra	25 – 50 mg
Ivabradine	Corlentor	10 – 20 mg
Rosuvastatin	Crestor	10 – 40 mg
Clopidogrel	Plavix	75 mg

The statistical analysis was performed with a comparator group of 288 subjects, matched with study group, with the same demographic features and medical profile, treated with current state-of-the-science medication. In order to test the therapeutic efficacy, and respectively the safety and tolerability of this quadruple combo we studied two groups of patients, using a standard proportion of 144 and 288 patients, respectively. This propensity adjustment of 2:1 allowed an adequate statistical analysis. The vast statistical apparatus will not be presented here in order to avoid excessive charge of this paper.

RESULTS AND DISCUSSIONS

Our study results are displayed in terms of therapeutic efficacy, tolerability and safety in administration.

Therapeutic efficacy

These results are based on the following investigations performed in all subjects:

- three ECG tracings in initiation visit, at 3 and 6 months, respectively;
- two echocardiographic transthoracic standard examinations performed by accredited and experienced specialists using the device Agilent 4500, at initiation and at 6 months, respectively;
- three standard lipid biochemistry panels, at initiation, 3 months, and 6 months, respectively, performed in accredited laboratories at high quality standards;
- the administration of quality of life questionnaire EQ-5D with thermometric scale from 1 to 100, at initiation and 6 months, respectively.

The results of our study in terms of therapeutic efficacy are synoptically presented in table no. 2.

Table no. 2. Therapeutic efficiency at 3 months and 6 months

Variable/Visit	0 (initiation)	3 months	6 months
SBP	126 +/- 12 mm Hg	118 +/- 11 mm Hg	111 +/- 10 mm Hg
DBP	79 +/- 7 mm Hg	71 +/- 6 mm Hg	70 +/- 6 mm Hg
PP	47 +/- 4 mm Hg	47 +/- 4 mm Hg	41 +/- 3 mm Hg
HR	108 +/- 11 beats/ min	90+/-9 beats/min	78 +/- 8 beats/min
LVEF	41,38%	-	46,77%
Total Seric Cholesterol	271 +/- 25 mg/dL	229 +/- 20 mg/dL	192 +/- mg/dL
LDL-Cholesterol	149 +/- 12 mg/dL	116 +/- 10 mg/dL	108 +/- 9 mg/dL
HDL-Cholesterol	35 +/- 5 mg/dL	38 +/- 5 mg/dL	37 +/- 5 mg/dL
Seric Triglycerides	202 +/-17 mg/dL	188 +/- 16 mg/dL	181 +/- 16 mg/dL
Nr. of strokes	-	0	1
Quality of Life Score	54,72%	-	71,14%
Oedema Decrease	+++	0/+	0/+

The blood pressure values evolution is interpreted in the clinical context of heart failure with severe systolic dysfunction. The combo preserves the body's homeostatic capacity to adequately react during various settings. We observe a slow and steady decrease of systolic blood pressure (SBP) during the 6 months of study, a slow decrease during the first 3 months and quasi-steady keep-on during the other 3 months of diastolic blood pressure (DBP), and a steady pulse pressure (PP) during the first 3 months followed by a decrease in the following 3 months. It is important that the combo moderately lowers the SBP, preserving the DBP in a convenient range for an adequate coronary perfusion.

It is also a remarkable result the steady and substantial decrease of heart rate (HR) during the study, documented on the surface 12 leads standard ECG, and mainly due to ivabradine.

In table no. 2, there is also presented a significant increase with 5 percents of the left ventricular ejection fraction (LVEF), parameter which reflects a substantial improvement of the systolic cardiac function. According to the data in the literature, this beneficial increase of the LVEF seems to be due to ivabradine and eplerenone. The efficacy in total and LDL-cholesterol lowering, the HDL-cholesterol rising, and the seric triglycerides lowering is clearly due to rosuvastatin. In case of total cholesterol we remark the achievement of international guidelines targets, which is remarkable taking into consideration that the study participants are in HF. We also observe the HDL-cholesterol rise. The efficacy of clopidogrel is directly determined by measuring platelet aggregation. Because at that time we did not have such a device, we have estimated the clopidogrel efficacy by a semiquantitative method considering the number of new thromboembolic strokes detected in any vascular territory (e.g. myocardial, cerebral, mesenteric or renal infarctions, acute ischaemia of the limbs etc.) in patients followed during the study. We mention here just a single transient ischaemic attack in a septuagenary patient in the second half of the study, remitted without sequelae. The quality of life scores displayed on EQ-5D questionnaire, thermometric scale, display an increase of > 16%. In our vision, all four pharmacological agents contribute to this outcome.

Last, but not least, the oedema decrease is a parameter easy to observe, but less quantifiable. That is why we used a semiquantitative way, which displays that the quadruple combo therapy, mainly eplerenone, then ivabradine, improves oedema quickly and actually completely.

Tolerability and safety in administration

Eplerenone. Within the study group of 144 patients, we observed a single adverse event (AE) (0,69%) characterized by minor unilateral gynecomastia in dosage of 50 mg/day, reversible with treatment interruption. Apparently surprising, because eplerenone is an aldosterone receptor blocker more specific than spironolactone, where this AE appears more frequently. We consider this event non-significant for prevention, because:

- the incidence is very low, under 1%;
- the AE was reversible;
- the dosage used in the invention is considerably lower than the dosage used in the clinical trial.

Ivabradine. During the study, we identified five AEs (3,47%) manifested by asymptomatic sinus bradycardia with HRs included in the interval 45-49 beats per minute with maximal dosage of 20 mg per day, all quickly reversible at drug down-titration with 10 mg per day. The significance of these events for prevention is minor, because:

- no symptoms;
- the AEs were quickly reversible;
- the dosages used in study were double till quadruple compared with preventions ones.

Rosuvastatin. Three AEs were registered (2,08%) manifested by muscle pain. In one of this subjects (0,69%) the laboratory displayed small and transient increments of hepatic biomarkers values (ALAT, ASAT). The significance of these AEs is minor, in our opinion, for the following reasons:

- very low incidence;
- the AEs appeared only in maximal dosage of 40 mg, which is 8 times higher than the dosage used in prevention dosages;
- all AEs were quickly reversible after treatment interruption, at 3-5 days;
- after restarting the treatment dosage of 10 mg we did not observe any troubles.

Clopidogrel. We did not report AEs in our study with this pharmacologic agent.

A synapsis of the AEs is presented in table no. 3.

Table no. 3. Synthesis of the adverse effects of the pharmacological agents used

Drug	AE	Prevalence	Symptomatic	Reversible	Which dosage?	Prevention dosage
Eplerenone	gynecomasty unilateral	0,69%	no, indolor	yes	50 mg	10-15 mg
Ivabradine	sinus bradycardia	3,47%	no	yes	20 mg	4-6 mg
Rosuvastatin	myalgia	2,08%	yes	yes	40 mg	4-6 mg
	positive biomarkers	0,69%	no	yes	40 mg	
Clopidogrel	-	0 %	-	-	75 mg	60-90 mg

We mention that, in this clinical study, the four drugs, clopidogrel, ivabradine, rosuvastatin, eplerenone were used in therapy. Clopidogrel, which did not present in this study AEs, is used in project frame in the same dose. Ivabradine, rosuvastatin and eplerenone displayed during the study, at high therapeutic doses, sporadic and rapidly reversible AEs. Please notice that, in this project, ivabradine, rosuvastatin, eplerenone are used in prevention in doses as ½-1/4, ½-1/8, and, ½-1/4, respectively, as those used in clinical study, so the probability of some AEs at this minidoses is insignificant. However, extended studies are needed to confirm our results.

CONCLUSIONS

According to reference sources, there are only minor interactions in vitro between eplerenone and clopidogrel. There is no mention in the literature about any eventual interaction between eplerenone, ivabradine, rosuvastatin, clopidogrel. From this state-of-the-science we started this study. The results of this study display the efficacy and safety of the combo therapy eplerenone, ivabradine, rosuvastatin, clopidogrel in therapeutic dosages in human subjects. Based on our clinical experience, we consider that, these four pharmacological agents could be associated into a fixed combination. Thus, the four molecules, clopidogrel, ivabradine, rosuvastatin, eplerenone could pharmacologically cohabitate in a single capsule. Moreover, the dosages used in this preventive goal being considerably lower, the risk of eventual AEs or drugs interactions is practically insignificant. Based on results of efficacy and safety, we consider that this quadruple combo could become, in adjusted doses, a polypill for CV prevention with high protection.

BIBLIOGRAPHY

1. Komajda M, Böhm M, Borer J, Ford I, Krum K, Tase A, Tavazzi L, Swedberg K. Influence of background treatment with mineralocorticoid receptor antagonists on ivabradine's effects in patients with chronic heart failure, European Journal of Heart Failure, Vol 15, number 1, January 2013, ISSN 1388-9842 pgs. 79-84. www.eurjhf.oxfordjournals.org.
2. Libby P, Bonow RO, Mann DL, Zipes DP. Braunwald's Heart Disease, A Textbook of Cardiovascular Medicine, Ninth Edition, Saunders; 2011.
3. Pitt B. Aldosterone blockade and heart failure, 2003;348:1380-1382.
4. Swedberg K, Komajda M, Boehm M, Borer JS, Ford I, Dobost-Brama A, Lerebours G, Tavazzi L, SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet 2010 Sep 11;376(9744):875-85.
5. Tase A, Brojboiu M. Combinaţie farmaceutică pentru prevenirea bolilor cardiovasculare, in press, OSIM, 2013.
6. Tase A, Ţeţiu O, Mihăilă M, Stănciulescu G, Trache C, Blăjan D. A 24 Months Study with Eplerenone Add-On AntiArrhythmic PharmacoTherapy Reducing the Occurrence of Atrial Fibrillation Episodes, Circulation online, World Congress of Cardiology Scientific Sessions Beijing, China; 2010.
7. Waldman SA & Terzic A. Pharmacology and Therapeutics. Principles to Practice, Saunders Elsevier; 2009.
8. Zannad F, et al, on behalf of EMPHASIS-HF Investigators EMPHASIS-HF: Eplerenone shows large benefits in milder heart failure, N Engl J Med, November 14; 2010.